REMARKS

Claims 5, 7-11, 13-28, and 32-36 are currently pending and under examination in the present application. Claims 1-4, 6, 29, 31 and 37-41 have been withdrawn. Claims 5, 7-28, 30 and 32-36 have been rejected. Claims 12 and 30 have been cancelled. Claims 42-48 were added by way of amendment dated July 13, 2005 filed in response to the Final Office Action of January 9, 2003. Claims 12 and 42-48 are cancelled in the present amendment. Claims 5, 7, 8, 11, 13-28, and 32-36 are amended herein and are therefore under examination pending entering of the present amendment.

Amendments to the Claims and Support Therefor

Claim 5 has been amended to recite that the target molecule complex is comprised of multiple linked individual units. Support for this amendment is found on page 25, lines 14-15 of the specification where it is stated that: "Simple multiples of this structure are shown in Figure 4 and are supported by the data depicted in Figure 5 generated by mass spectroscopy analysis." In Figure 5, the mass spectra of the complex comprising the bridging component, chromium, and the complexing component N-(2,6-diisopropylphenyl carbamoyl methyl)iminodiacetic acid indicates that individual units are linked together. Figure 4 depicts a graphical representation of the mass spectra where the individual units are linked together. Claim 5 has also been amended to specify that the individual units are comprised of a bridging component and a complexing component. Support for the bridging "component" is found in Figure 3 of the specification, where chromium is a component of the individual unit. Support is also found on page 13 line 32 to page 14 line 1 of the specification, which states "A suitable metal compound that is the selected bridging agent intended to be complexed with the complexing agent, is one which is soluble in water and capable of forming a coordinated complex with the aforementioned hepatocyte directed molecules." By forming a coordinated complex, the metal becomes a component of the target molecule complex. Support for the complexing "component" is found in Figure 3 in the specification, where N-(2,6-diisopropylphenyl carbamoyl methyl)iminodiacetic acid is a component of the individual unit. Support is also found on page 8 lines 1-4 of the specification where it is stated that: "A suitable complexing agent is one which will complex with a selected bridging agent ... to form a complex of such metal". By forming a complex, the

complexing agent becomes a component of the target molecule complex. Applicants have also amended Claim 5 to correct a simple grammatical error, by replacing "An" with "A".

Claim 7 has been amended to add "system comprising the hepatocyte-specific target delivery" to distinguish a target delivery molecule, that lacks a pharmacological, therapeutic, or diagnostic agent, with a targeted delivery system which contains a pharmacological, therapeutic, or diagnostic agent. Support for this amendment is found in the Field of the Invention section of the specification on page 1, lines 5-9 of the as filed application where it is stated that: "This invention pertains to metal complexes, ..., and to targeted liposomal drug delivery systems containing the complexes, particularly to those useful for the delivery of an agent to the hepatocytes of the liver." Claim 7 has also been amended to correct a minor typographical error to replace "The" with "A".

Claim 8 has been amended to recite that the agent is associated with the liposome matrix. Support is found on page 16 lines 8-9 of the specification, where it is stated that: "Typically, the pharmacological agent is encompassed by the liposomal matrix or entrapped in the liposomal core volume."

Claim 11 has been amended to add proper Markush language and to add a mixture of any of the foregoing lipids as one of the Markush groups. Support for a mixture of lipids is found on page 15 lines 8 and 11 in the as filed application.

Claim 13 has been amended to depend from claim 5 and to replace "targeting" with "target delivery" to have antecedent basis in claim 5 from which claim 13 depends. Claim 13 has also been amended to recite that the bridging component is chromium. Support for this amendment is found in the specification on page 5, lines 26-27.

Claim 14 has been amended to depend from claim 5, to replace "targeting" with "target delivery" and to replace "agent" with "component" to have antecedent basis in claim 5 from which claim 14 depends.

Claim 15 has been amended to depend from claim 5, to replace "targeting" with "target delivery" and to replace "liposomal membrane" with "liposome matrix" to have antecedent basis in claim 5 from which claim 14 depends, to insert a comma, and to add proper Markush language.

Claim 16 has been amended to insert a comma, and to replace "liposomal membrane" with "lipid" have proper antecedent basis in claim 15, from which claim 16 depends.

Claim 17 has been amended to insert a comma.

Claim 18 has been amended to recite that the target molecule complex is comprised of multiple linked individual units and to grammatically clarify the nature and relationship of three components which comprise the article of manufacture. Support for these amendments is identical to the support recited for claim 5.

Claim 19 has been amended to replace "agent" with "component" have proper antecedent basis in claim 18, from which claim 19 depends.

Claims 20 and 21 have been amended to insert a comma to more properly clarify the meaning of the claim and to replace "the" with "said" to use consistent language in the claims.

Claim 22 has been amended to recite that the target molecule complex is comprised of multiple linked individual units, and to clarify that the delivery system contains an active agent which is delivered to hepatocytes. Support for these amendments is identical to that recited in claim 5.

Claims 23 and 24 have been amended to insert a comma to more properly clarify the meaning of the claims.

Claim 25 has been amended to replace "bridging agent" with "target molecule" to have antecedent basis in claim 22 from which claim 25 depends, and to insert a comma to more properly clarify the meaning of the claims.

Claims 26 and 27 have been amended to insert a comma to more properly clarify the meaning of the claims.

Claim 28 has been amended to replace "being composed of" to "comprising" to properly recite the claim and to replace "preferentially loads into the core or into the membrane or onto the surface of said liposome for delivery to the hepatocytes in the liver of a warm-blooded host" with "is associated with said liposome". Support for this amendment is found on page 16 lines 27-28 of the specification which states: "where at least one of the derivatives preferentially loads into the core or into the membrane or onto the surface of the liposome ...".

Claim 32 has been amended to replace "which comprises, a transport agent comprising a liposome having associated therewith a bridging agent selected from a metal complex, a dissociated form thereof or a water insoluble polynuclear complex or a mixture of any of the foregoing; where said dissociated form exists with or without metal present in said liposome; provided that when compound chromium is used, it is present as a chromium target molecule

complex or a dissociated form thereof" with ", wherein said composition comprises a hepatocyte-specific target delivery molecule comprising a water insoluble target molecule complex, wherein said complex comprises multiple linked individual units and a liposome matrix, said multiple linked individual units comprising: a bridging component selected from the group consisting of a transition element, an inner transition element, a neighbor element of said transition element and a mixture of any of the foregoing elements, and a complexing component, provided that when said transition element is chromium, a chromium target molecule complex is created, wherein said multiple linked individual units are combined with said liposome matrix". Support for this amendment is identical to the support recited for claim 5.

Claim 33 has been amended to replace "as defined in" with "of" to properly recite the claim, to insert a comma to more properly clarify the meaning of the claim, to add the word "matrix" to have antecedent basis in claim 32 from which claim 33 depends, and to add proper Markush language.

Claim 34 has been amended to replace "as defined in" with "of" to properly recite the claim, to insert a comma to more properly clarify the meaning of the claim, to depend from claim 33 rather than claim 32, and to replace "liposome" with "lipid" to correctly describe the members of the Markush group and to have antecedent basis in claim 33 from which claim 34 depends.

Claim 35 has been amended to replace "as defined in" with "of" to properly recite the claim, to insert a comma to more properly clarify the meaning of the claim and to add "matrix" to have antecedent basis in claim 32 from which claim 35 depends.

Claim 36 has been amended to insert a comma to more properly clarify the meaning of the claim and to add proper Markush language.

No new matter has been added by way of any of these amendments.

Remarks

The present application was originally filed on May 18, 1999. The present amendments to the claims are made in response to the Final Office Action dated January 9, 2003 and are supplemental to and supersede the amendments made in response to the Office Action filed on July 13, 2005.

The undersigned has Power of Attorney in the present application way of a Revocation and Power of Attorney filed in the Patent Office on September 21, 2005.

Applicant respectfully requests the Examiner's consideration of the amended claims and would appreciate the Examiner's time for an interview with the undersigned in order to discuss the same.

Applicants remarks concern the Examiner's rejection of the claim in the Office Action dated January 9, 2003.

1. Claims 5, 7-28, 30 and 32-36 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Geho (WO 88/00474 and US 4,603,044).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Examiner states that the referenced patents disclose liposomes containing either Cr, Co, Fe or Zn complexed with iminidiacetic acid derivates. According to the Examiner, the liposome further contains either insulin or serotonin.

The present claims are distinct from both WO 88/00474 and US 4,603,044 in that the claims in the present application recite that the target molecule complex is water insoluble and is comprised of multiple linked individual units, where the individual units are comprised of a bridging component and a complexing component.

These elements are not disclosed by Geho in either WO 88/00474 or US 4,603,044. Rather WO 88/00474 and US 4,603,044 teach a water soluble complex and disclose a structure where only an individual unit is produced. The complex described in WO 88/00474 and US 4,603,044 is an individual unit, not multiple linked units, as recited in the present claims. Furthermore, the complex of WO 88/00474 and US 4,603,044 is water soluble, whereas the complex of the present invention is water insoluble. Therefore independent claims 5, 7, 13, 18, 22 and 32 and dependent claims therefrom can not be anticipated by either WO 88/00474 and US 4,603,044.

Applicants respectfully request reevaluation and withdrawal of the rejection of claims 5, 7, 13, 18, 22 and 32 under 35 U.S.C. § 102(b) as being anticipated by WO 88/00474 and US 4,603,044.

2. Claims 5, 13, 22, 24, 32, 33 and 35 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bosworth (US 5,407,660). The Examiner opines that Bosworth discloses liposomes containing chelates of iron for diagnostic applications. Further, according to the Examiner, the liposomes contain cholesterol.

The current claims in the present application are distinct from US 5,407,660 in that amended Claims 5, 13, 22, 24, 32, 33 and 35 in the present application recite that the complex is water insoluble and is comprised of multiple linked individual units, where the individual units comprise a bridging component and a complexing component. The chelates disclosed by Bosworth are water soluble. [column 3, line 23] Bosworth does not disclose a complex comprising multiple linked units. Claims 5, 13, 22, 24, 32, 33 and 35 recite that the complex is water insoluble and is comprised of multiple linked individual units; therefore these claims are not anticipated by US 5,407,660.

Applicants respectfully request reevaluation and withdrawal of the rejection of claims 5, 13, 22, 24, 32, 33 and 35 under 35 U.S.C. § 102(b) as being anticipated by US 5,407,660.

3. Claims 5, 13, 15, 18, 22, 24 and 32-35 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Baldeschwieler (US 4,310,506). The Examiner opines that Baldeschwieler discloses liposomes containing chelates of metals such as Cr, In, Co and Zn with iminodiacetic acid for diagnostic applications, where the liposomes contain distearoylphosphatdylcholine, dicetyl phosphate and cholesterol.

The current claims in the present application are distinct from US 4,310,506 in that amended Claims 5, 13, 15, 18, 22, 24, and 32-35 of the present application recite that the complex is water insoluble and is comprised of multiple linked individual units, where the individual units are comprised of a bridging component and a complexing component. The specification (page 2. lines 13-16; page 15 lines 7-10) of the present application teaches the use of a liposome with a water insoluble complex comprised of multiple linked individual units that exhibits the chemical property of dissolving into the liposome structure. The liposome delivery disclosed by Baldeschweiser comprises water-soluble chelates that are carried in the liposome's aqueous core ("trapped within the vesicles" (column 2, lines 8-13), where "vesicles" refers to small sacs containing fluids. column 2, lines 64-65)). Baldeschweiser distinguishes an ionophore being incorporated in a lipid bilayer, from a chelating agent entrapped within the vesicles.

(column 2, lines 9-11). Baldeschweiser does not disclose a water insoluble complex comprising multiple linked units. Since Claims 5, 13, 15, 18, 22, 24 and 32-35 of the present application recite that the complex is water insoluble and comprised of multiple linked individual units, these claims are not anticipated by US 4,310,506.

Applicants respectfully request reevaluation and withdrawal of the rejection of claims 5, 13, 15, 18, 22, 24 and 32-35 under 35 U.S.C. § 102(b) as being anticipated by US 4,310,506.

SUMMARY and CONCLUSION

The foregoing amendments and remarks overcome or render moot all grounds for rejection put forth by the Examiner. There being no other rejections, this application should be in condition for allowance. Applicants therefore respectfully request prompt action and allowance of the claims.

Respectfully Submitted,

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(Date)

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